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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE
DISEASES OF INFANTS AND CHILDREN
JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

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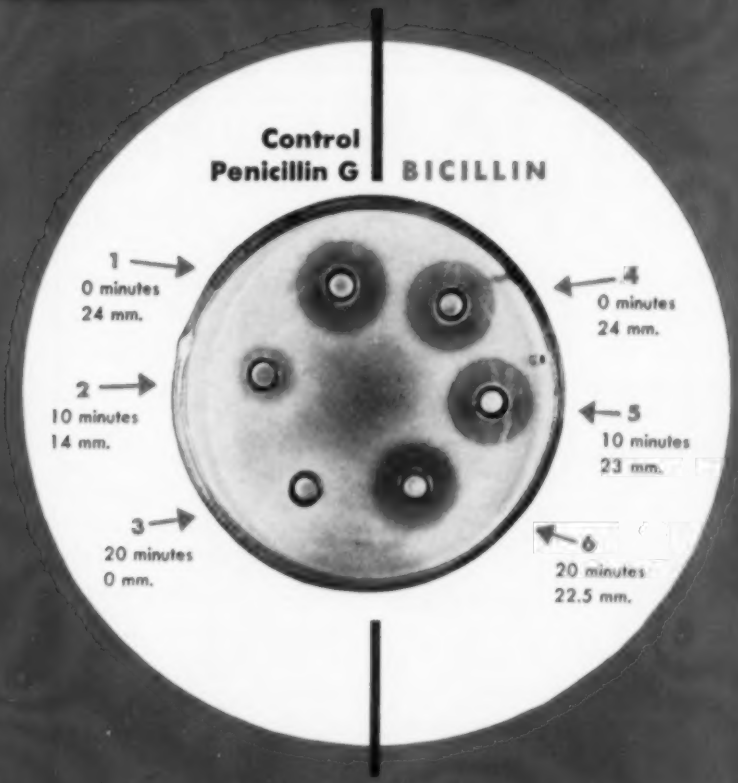

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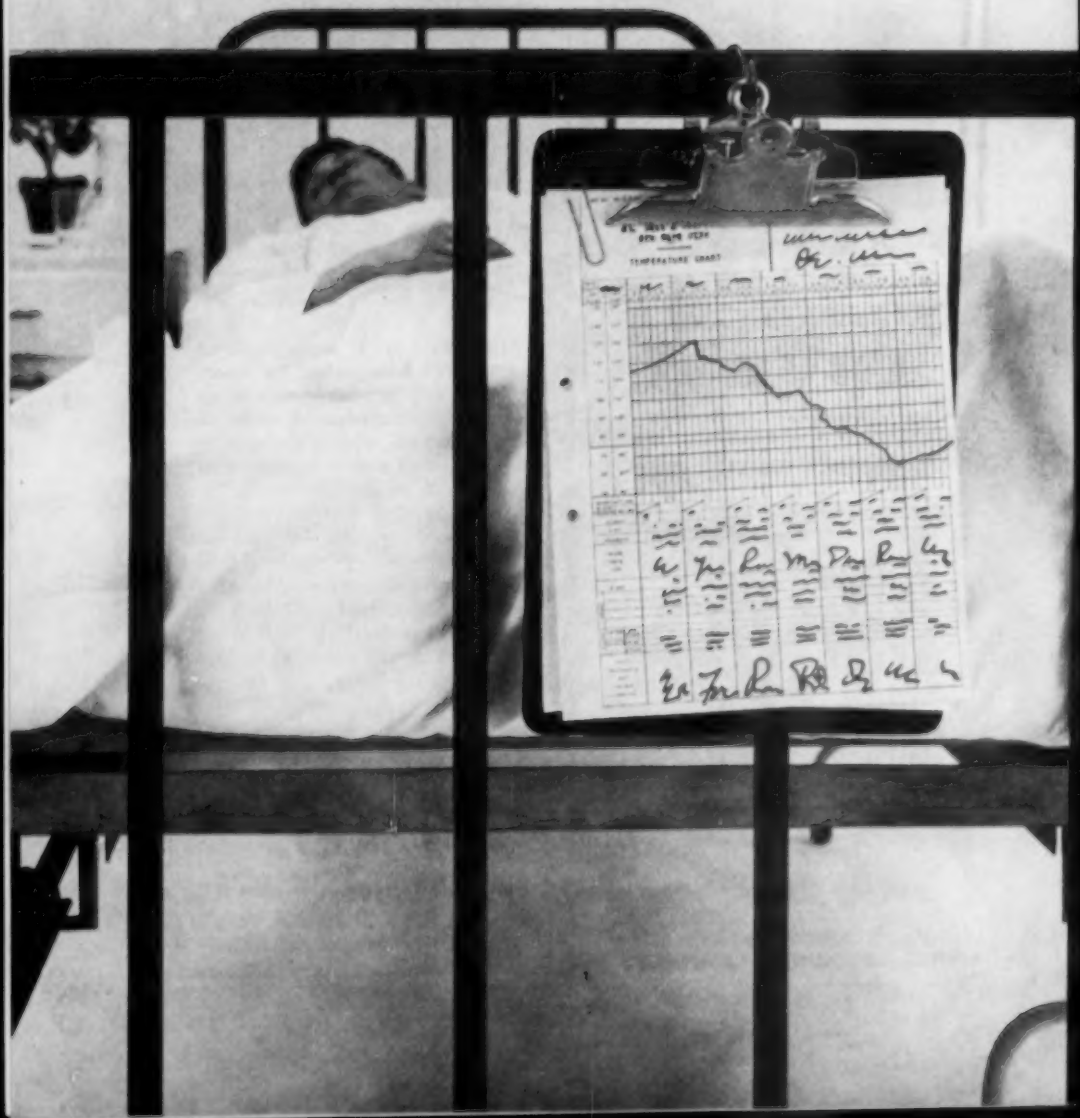

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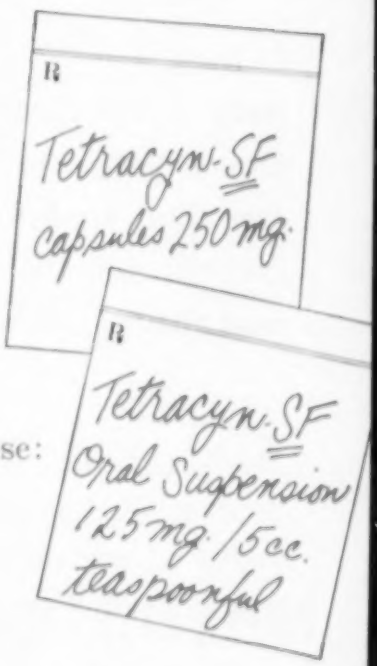

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NOTES ON CYANOGENETIC GLUCOSIDES AND OTHER CYANOUS MATERIAL AS THEY APPEAR IN NATURE AND THEIR POSSIBLE RELATIONSHIP TO ANTERIOR POLIOMYELITIS

HERMAN C. AMSTER, Ph.G.
Jamaica, N. Y.

Plant ecology has produced evidence that variations occur, not only in the physical nature of plants and their fruits, but also in their chemical characteristics. It is now a definite part of our understanding of plant life that these changes do not necessarily occur in a true pathological sense where the plant is affected by parasite, fungus or virus. It has been noted that the physical and chemical structure of a plant can be greatly affected by types of soil, climate and altitude.

Throughout medical history there is evidence of poisoning of man by ingestion of certain foods which are normally harmless. Many of these foods contain, encased in harmless form, cyanous materials. These compounds usually are found as cyanogenetic glucosides. Under certain conditions, these cyanogens are converted into toxic cyanides, producing symptoms of poisoning.

The more commonly known sources of these cyanogens are:

1. *Dhurra wheat* (sorgum vulgara): commonly used in the production of Kaffir bread in Africa. Many cases of cyanide poisoning have been reported because of the decomposition of the amydalin (cyanous) present in the Dhurra wheat.

2. *Lima bean* (phaseolus lunatus *or* phaseolus limenses): under

certain adverse conditions of growth, ecological studies have shown harmful quantities of hydrocyanic acid develop from cyanogens contained in the bean. Dunlop, in 1917, reported that Phaseolus Lunatis produces a variant, the Java bean, which is highly toxic. The toxicity of the bean depends upon phaseolunatin, a cyanogenetic glucoside, which forms hydrocyanic acid in the stomach. The principal United States bean-producing states are Michigan, California, Colorado, New Mexico, New York and Idaho.

3. The family *Rosaceae and Pomaceae:* here the cyanogenetic glucosides are widely diffused, covering a wide range of fruits, such as the apple, pear, strawberry, blackberry, in all of which the cyanogenetic content is minute, and the almond, peach, cherry, plum and salmonberry, in which the cyanogenetic compounds appear in large percentages. The peach, cherry, plum and almond are found in the temperate zones. The salmon- or cloud-berry is found and used chiefly in Alaska and in the northern tundra. The salmonberry is an important native Eskimo food. Used fresh or preserved in seal oil, it is practically the only plant food available to the Eskimos. It is to be noted that, despite the extensive diffusion of these cyanogenetic foods, very few cases of poisoning of this nature have been reported. Yet, as far back as 1830, when Robiquet and Bouton discovered amygdalin, the most widespead cyanogenetic glucoside, it was observed that amygdalin is quickly decomposed by: (a) dilute acids; (b) the ferment "emulsin" in the presence of water; (c) ferments present in ingested foods in the alimentary canal.

These hydrolyses are illustrated as follows:

$$\underset{\text{(Amygdalin)}}{C_{20}H_{27}NO_{11}} + H_2O = \underset{\text{(Glucose)}}{C_6H_{12}O_6} + \underset{\text{(Mandelonitrile Glucoside)}}{C_{14}H_{17}O_6N}$$

$$C_{14}H_{17}O_6N + H_2O = C_6H_{12}O_6 + \underset{\text{(Benzaldehyde}}{C_7H_6O} + \underset{\text{(Acid-Hydrocyanic)}}{CNH}$$

Amygdalin itself is practically non-toxic, but when ingested may be decomposed as described above, leading to the formation of

hydrocyanic acid and thus producing the toxic symptoms of prussic acid poisoning. In the light of the instability of amygdalin and the constant presence of this glucoside in worldwide diet, it would seem that more cases of this type of poisoning should be reported. It is possible that physicians may be diagnosing this toxicity as anterior poliomyelitis. It is the considered opinion of this observer that much of the confusion of the current poliomyelitis program has been the inability of diagnosticians to differentiate between the paralysis or paralytic symptoms produced by the slow release of cyanides in normally harmless cyanogens from those produced by the anterior poliomyelitis virus.

A comparison of symptoms of poisoning by the slow release of cyanides from cyanogenetic glucosides and that of anterior poliomyelitis shows them to be identical. They are: (1) sense of constriction of the throat; (2) salivation and nausea; (3) vertigo and headache; (4) respiration, first rapid, then slow and irregular; (5) pulse first bounding, then slow; (6) pupils dilated, insensible to light; (7) skin cold; (8) blood darkens as in asphyxia; (9) in moderately acute cases, the blood is bright scarlet.

Absence of vomiting and purging is to be noted, indicating desensification of the stomach reflexes. Note also should be taken of the sudden onset and non-progressive nature of both types of paralysis. This is atypical of usual bacterial or virus infection.

Both the symptoms of poliomyelitis and cyanide poisoning are rooted primarily in the respective centers of the medulla where increased activity suddenly takes place. This increase in activity is the result of reduced oxidative processes in the medullary centers and is followed by depression, ultimate degeneration of the central nervous system and paralysis. Whether the symptoms stem from anterior poliomyelitis or insidious cyanide toxicity, the results are the same.

In both conditions there is an acute inflammation of the spinal motor neura of the anterior cornua.

It is important, then, that diagnosticians, upon observing the above symptoms, be aware of the fact that they may not only be faced with the possibility of anterior poliomyelitis but also by a case of concealed cyanide poisoning.

The diagnostician, in order to differentiate, should proceed by:

(1) Testing the stomach contents for cyanogens. (2) Analyzing blood and urine to determine if they have become cyanous.

In order to complete the comparison of anterior poliomyelitis history and that of cyanogenetic glucosides as they appear in nature, the following should be noted:

(1) The seasonal and geographical nature of both conditions: (a) In cyanogen poisoning there is a direct relationship to availability of amygdalin-bearing foods, the supply of which is dependent upon geography, season, harvesting and ecological factors. (b) In anterior poliomyelitis there is a seasonal and geographic pattern evident, but the relationship is still unexplained.

(2) The age limitations of those affected: In examining the age limitations of those afflicted with anterior poliomyelitis or cyanide poisoning, posology and toxicology point to the direct relationship of the age-weight formula in the dosage effect of toxins upon the human body. By pursuing the proven age-weight formulas of posology, the deleterious effects of both pathologies can be measured directly by the age and weight of the patient. The paralysis, death or recovery can likewise be linked to a relationship between the quantity of toxins, either created by the poliomyelitis virus, or ingested in the form of cyanogenetic glucosides.

SUMMARY

In summation, there is evidence that paralysis or paralytic symptoms can be caused by: (1) the poliomyelitis virus; (2) the introduction into the body of cyanogenetic glucosides contained in plant foods which may have been affected by chemical changes because of environmental factors. The most important cyanogen-bearing foods are the lima bean, the almond, the peach, the plum, the cherry, the salmonberry and their variants. They have been known to produce as much as three per cent hydrogen cyanide.

It is important, therefore, that all poliomyelitis examinations include analysis for cyanides or cyanogen in the stomach, urine and blood. If examination shows the presence of cyanous compounds, the following is indicated: (1) the stomach should be emptied; (2) ferric salts, particularly in the form of ferri hydroxide cum magnesium oxide should be given; (3) in more advanced cases, sodium thiosulfate may be supplemented; (4) in 1933, Turner and

Hulpieu suggested intravenous use of dihydroxy acetone to ameliorate symptoms and to permit a sufficient time for the antidotal effect of the thiosulfate to take place.

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PREVENTION OF HYALINE MEMBRANE AFTER CESAREAN SECTION. (M.J. Australia, 2:386, Sept. 4, 1954). Hyaline membrane is one of the major causes of death in infants delivered by cesarean section. The Boston theory is that hyaline membrane is the result of aspiration of amniotic fluid into the respiratory tract and the precipitation of the protein content in the alveolar duct. A baby delivered by cesarean section is in great danger of inhaling this fluid, and so Pash decided that an attempt should be made to suck out the respiratory passages of the baby before this aspiration could take place. After the incision into the lower segment, blood and liquor are sucked away, and the excess is removed by swabbing. If the head is low, the baby is usually delivered by the face, and in this case the assistant, as soon as the mouth is accessible, places a catheter in the mouth, and mouth and pharynx are cleaned before the child's head is delivered. This suction is maintained throughout the delivery of the head, and sucking out of the mouth and pharynx is continued while the child's body is delivered, and then the child is held with its head down. As soon as the cord is clamped and cut, the assistant, carrying the child with the head low, takes it to a cot, which is inclined with head down at an angle of 30 degrees, and the stomach is then emptied of ingested liquor with a mucus catheter. If the head is high, suction is instituted as soon as the mouth is accessible, and delivery is delayed until the airway is reasonably clear. With the use of this method there were no deaths from hyaline membrane in 60 elective cesarean sections.—*J.A.M.A.*

TREATMENT OF KIMMELSTIEL-WILSON DISEASE AND RELATED CONDITIONS*

FREDERICK M. ALLEN, M.D.
New York.

The Kimmelstiel-Wilson name denotes a renal-vascular pathologic process which is progressive intrinsically after its diabetic origin. It is a pediatric problem, because the source is so often traceable to childhood, even to early childhood as in the case here reported. Retinopathy with blindness is frequent in the juvenile years. The renal lesions, usually with, but, occasionally without the retinal lesions, may appear in youth or reach their severity only in early or middle adulthood. These and other vascular degenerations are to be regarded as consequences of inadequately controlled diabetes. The renal condition, however, is familiar at a stage where neither control of the diabetes nor any other known treatment arrests the fatal progression to uremia. The incidence has risen until it now accounts for an important proportion of diabetic deaths. The present proposal of a new principle of treatment requires an introductory discussion of three topics, namely nephritis, hypertension and some metabolic relations of the kidneys.

Experiments on Nephritis. This is a brief notice of the kidney experiments of our Morristown group, which followed the general lines of my earlier diabetic research,[1] using partial nephrectomy as analogous to partial pancreatectomy. At that time, the primitive claims[2] of reproducing chronic nephritis by this means had been discredited, and there was universal acceptance of the teachings of Pearce, Janeway[3] and others that the result was either acute death or practically normal survival. With early observations on the feeding of protein and salt to such animals,[4] we were the first to show[5] the complete reproduction of the picture of chronic nephritis, including albuminuria, hyposthenuria, azotemia, acidosis, blood volume changes, anemia and microscopic renal pathology. Edema is slight and difficult in dogs but was easily obtained in sheep. Hypertension is slight in dogs, which die acutely from removal of slightly over three-fourths of the total renal tissue; but Chanutin,[6] using rats, furnished the first demonstration that when greater

*Paper read before the American Diabetes Association, Atlantic City, N. J., June 5, 1935.

amounts of kidney tissue can be removed the hypertension is greater. My method of auscultatory blood pressures in dogs[7] lately has been confirmed and improved by Wilhelmj.[8] Also, by making the first kidney explantations,[9] we noted changes in size with different diets. Dr. Robert Mark[10] of our group, now a professor at Rostock, Germany, added the important observation of retinitis. Dr. Millard Smith went from our group to Dr. Joslin's clinic, where he demonstrated the lowest known nitrogen metabolism,[11] which is valuable for the present paper. Beginning in 1922 we studied a hypotensive vasodilator kidney extract, but refrained from publishing such claims as were made by various subsequent workers. This extract was taken over and further purified by Jablons,[12] who obtained priority over subsequent writers.

Our principal unpublished work concerned dogs nephrectomized to a border-line state in which their fate depended on diet. The albuminuria and renal pathology produced by Medlar-Blatherwick[13] and others with high protein diet in normal animals of some species appear unrealistic, because renalvascular lesions have not resulted in carnivorous peoples such as the Eskimos. But the properly prepared dogs, with a slight overload of protein or salt, can show a gradual progress into fatal uremia, or with absence of overload they have no progression. Dr. Sidney Bliss adopted one of these dogs as a pet, keeping it on minimum protein and without salt. The results correspond to the earlier ones with partial pancreatectomy. There is the same question as in diabetes: Is the downward progress in human cases similarly controllable, or is there an inherent factor of progressiveness?

Hypertension. The first permanent partial ligations of renal arteries or veins for a metabolic purpose were those which I published[14] in 1923, without observations of blood pressure. Pedersen,[15] in 1927, obtained more or less hypertension by such partial ligations of renal veins in rabbits, and then Goldblatt,[16] in 1934, developed the arterial ligation which became the standard method for experimental hypertension.

I had described our various lines of experimentation before the congress on kidney diseases at Minneapolis in 1932 (though this half-hour presentation was entirely omitted from the published

proceedings[17]). I failed to follow up the permanent partial ligations, giving preference to temporary complete ligations like the pancreatic ligations which produced diabetes.[18] Contrary to what various writers have described in anesthetized animals, the stoppage of blood flow to the kidneys of a normal comfortable animal results in marked immediate hypertension, which subsides after restoration of circulation. The role of pressor substances from the ischemic kidney, is not, therefore, what these writers supposed, or else it can be counterbalanced by other factors. But the chronic hypertension described by Loesch[19] proved to be slight or undependable, and multiple ligations produced only interstitial, not the hoped for glomerular lesions.[20]

The clinical work was more successful. The announcement of saltless diet in 1920[21] was expanded in 1922 to a report of 186 cases treated for periods up to four years.[22] This was the first accurate exclusion of salt for hypertension, congestive failure and retinitis, and the first in this country for puerperal eclampsia. Though I exposed blunders[23] in the attacks from leading clinics, the treatment was suppressed by weight of authority for over twenty years. Confusion has been caused chiefly by the fact that a minority of hypertensions show no early response, though the benefits usually become evident in the course of years. Our 4-year statistics in 1922 showed about 30 per cent of cases to be thus "refractory." Kempner[24] confirmed the general resluts, and in a 4-year experience with his more onerous diet, he recorded the same 30 per cent of "refractory" cases.

Some Metabolic Relations of the Kidneys. Protection against alloxan diabetes by clamping of renal pedicles was attributed by Arteta[25] to a nerve reflex. A somewhat opposite finding is that nephrectomy augments the diabetogenic action of alloxan (De Oya, Diaz and Grande[26]). A gluconeogenic function of the kidney has been claimed[27] and denied.[28] The association of diabetes with so-called nephritis was familiar in early literature, and German authors noted the amelioration of the diabetes in some instances. This observation has lately been confirmed by Zubrod,[29] with evidence that as intercapillary glomerulosclerosis progresses, the diabetic glycosuria and ketosis diminish. In 1923 it was found that the susceptibility of dogs to ketosis with fasting and phloridzin was not altered

by the Eck fistula.[20] But kidney injuries, in the form of partial or total nephrectomy, ligation of ureters or partial ligation of veins or arteries, markedly reduced glycosuria, hyperglycemia, D/N ratios and ketosis in both phloridzin glycosuria and pancreatic diabetes.[14] This might be expected with phloridzin. But I had been the first to discover the fatal ketosis which develops in normal young puppies on simple fasting,[21] and the renal disturbances also reduced this form of ketosis. Ketonemia always diminished along with ketonuria, but no increased ketolytic power was demonstrated with acetone body injections. If, in retrospect, it can be assumed that the dogs with permanent partial ligation of renal arteries were hypertensive, the reproduction of the Kimmelstiel-Wilson syndrome appears still closer. At any rate, a means of experimental study of the influence on glycosuria and ketosis has long been available. It points to a role of the kidney in intermediary metabolism.

My excuse for such a predominantly personal review of contributions and priorities is that most of it is unknown to you. My publications after 1919 remained practically unmentioned in the literature except when the hypertension treatment was attacked.

Therapy. Since 1914 I recognized that progression is the basic problem of diabetic treatment. I have been the first, and most positive, in maintaining that diabetes is controllable in patients as dependably as in dogs.[22, 23] Today, there are some loose remarks that diabetics then had the choice of dying of diabetes, or starving and then dying anyhow. Such ignorance is displayed only by those who never kept a single undernourished diabetic with normal blood sugar. Rare cases, especially in children, were too severe for the sugar to be made normal, and those individuals died of either diabetes or starvation. Others, especially young adults, might have such severity of diabetes that control required starving them to skeleton thinness, but, if the blood sugar was kept normal, they survived to receive the benefits of insulin, along with the better nourished milder cases. With insulin, the question of progression has become one of complications. During 30 to 40 years I have never been accused of deception by any of the patients to whom I invariably promise freedom from complications if they follow treatment. I have also challenged others to show a typical complication without a history of marked departures from normal sugar.[23]

I think the truth should be driven home that every complication is the fault of somebody, either the doctor or patient. Likewise it would have been better if I had been permitted to continue the statistics, which were begun at Morristown in 1920, to settle the specificity of control by saltless diet in hypertension. My conviction, based on thirty-odd years of experience, is that progression and complications are prevented even in the seemingly refractory cases, except the few already in the malignant stage.[33] Notably, congestive failure terminates about half of cases in general, and no cases on saltless diet.

Intercapillary glomerulosclerosis combines features of diabetes and hypertension. While it is preventable by good diabetic control, after it has begun, there seems to be no definite information concerning stages where it may still be controllable, and the later stage where it is commonly seen, from which it progresses in spite of diabetic control or saltless diet, to end typically in uremia. The therapeutic question is, can this progression be prevented? There have been some reports of marked relief by adrenalectomy in this condition,[34] and also in simple severe hypertension, [35] as well as some encouragement with hypophysectomy.[36] These operations can scarcely restore a failing kidney function, and uremic tendencies are actually listed as contraindications. The main obstacle is that such a procedure requires a highly trained team working with exceptional facilities for the operative period, and meticulous care of the patient forever after. Therefore, the operations, still largely experimental, seem not to furnish a solution for the great mass of such patients throughout the country.

Here it is appropriate to recall the principle of the early diabetic treatment, namely, the reduction of body weight and metabolism to bring them within the capacity of an impaired function. For years past I have been thinking that diabetes was perhaps the least promising disorder for application of this principle. Some other diseases may respond better, if the details are modified to suit the respective needs. In diabetes, the tolerance is chiefly affected by increase or decrease of adipose tissue. Kidney function is essentially related to the protein mass of the body. During my own blockade by lack of facilities and opportunities, Borst,[37] in Holland, came nearest to this idea with a protein-free diet for rather long periods to combat

uremia. But, in general, all forms of protein restriction have failed to arrest progressive kidney disease, possibly because they considered only the excretory and not the intermediary metabolic kidney function. Nobody has formulated the new concept of reduction of body mass and metabolism as suggested by my nephrectomy experiments. Although all dogs die from removal of slightly more than three-fourths of their total kidney tissue, the tissue mass that is fatally inadequate for a Great Dane on any diet would be ample for a toy terrior. We may conceive of changing the patient from a big dog to a little dog, as regards protein tissue. The diabetic dogs had to be emaciated to skeleton thinness to control diabetes; but in kidney disease the highest possible non-protein nutrition minimizes nitrogen metabolism, while the protein intake is low enough to make a continuously negative nitrogen balance which assures continuous wasting of the protein tissues.

An opportunity to try this idea came only fortuitously. Early in 1922, a six-year-old Jewish boy was brought to Morristown with severe diabetes. His sugar and acetone were cleared up, and he was made thin and weak in order to maintain normal blood sugar. Later that year he was one of the first patients to receive insulin. At home, in an excellent state of nutrition, he was precociously bright, self-willed and soon unmanageable. He regulated his own diet in a way which many diabetic specialists approve, having only occasional moderate glycosuria and never a dangerous episode. He grew up normally, smoked cigarettes excessively, married and never missed a day from work on account of health. I saw him only three times in all the intervening years, when he would not permit even a blood analysis.

About a year ago, this patient began to have anginal pains. A doctor found albuminuria and hypertension, and prescribed a low-salt diet without protein restriction. He continued to work while his condition grew gradually worse, with occasional vomiting, until last October when he was hospitalized. There, the dilemma was that with 1 or 2 grams of dietary salt he had hypertension, marked edema and severe angina, and without salt he developed intolerable muscle pains and uremia. Mercurial drugs produced diuresis but increased uremic symptoms. An imminently fatal prognosis caused his family to bring him to me, in November 1954.

He was taking 15 or 20 nitroglycerine tablets daily, besides phenobarbital, and when I saw him he had to take a nitroglycerine tablet to control the angina brought on by speaking. He had uremic malaise, vomiting and nosebleeds, moderate albuminuria, considerable edema, blood pressure 210/110, pulse rate at rest 120, anemia of 2,800,000 red cells with normal leukocytes, basal metabolism plus two, blood urea nitrogen 215 mg. and creatinine 15 mg. per cent, with normal blood electrolytes. This is similar to the Kimmelstiel-Wilson picture, with the exceptions that the albuminuria was never heavy, the angina was extra, vision especially was perfect and several observers agreed that the eye grounds were normal.

The need of simplicity in a treatment, if it is to be serviceable for large numbers of cases throughout the country, was illustrated in this patient, who was unable to obtain hospitalization for the time that would be required and thus had to be treated entirely at home, with guidance only of occasional analyses from a commercial laboratory. The one asset was that he understood diet methods thoroughly and had become completely cooperative and dependable. At first, acute dangers had to be warded off by juggling salt intake, fluid volume and a few drugs. The essential treatment was a protein-free diet for two months, and for seven weeks after that a limit of 15 grams protein daily. The protein of fruits and coarse vegetables was ignored in the "protein free" period but was included in later calculations. They make such diets endurable for unlimited duration. Cane sugar, cornstarch and fats provided the principal calories, ranging irregularly from 2000 to over 3000 daily, without forcing. Cookies composed of cornstarch, butter and sugar, originally introduced at the Physiatric Institute, are a staple in such a diet. Both the minimal exogenous protein and the progressive decrease of endogenous metabolism gradually lightened the renal excretory burden, so that the blood nitrogen steadily diminished, and the uremic symptoms cleared up. With this came ability to tolerate a salt-free diet, calculated as 15 to 20 mg. of sodium daily, bringing freedom from edema and angina. By late February and March, the blood figures had fallen to 52 mg. urea nitrogen and 7.6 mg. creatinine.

At this time, namely, at the end of the 15-gram protein diet,

the patient "felt fine," was cheerful and seemingly energetic, but any exertion revealed muscular weakness. A walk of two or three blocks exhausted him. As he insisted on resuming light work for financial reasons, the protein was increased during March and April to 20, 25 and finally 30 grams. With this he regained considerable strength. He was able to take up his regular work as a salesman to business firms over a large territory, requiring him to drive his automobile about 75 miles daily. He also refused to give up membership in a volunteer fire company. He was still incapable of manual labor or heavy lifting. His normal weight and apparent nutrition must have been due to fat, which masked the wasting of muscles. Since healthy persons have been known to remain strong on these quantities of protein, the weakness is evidently due either to the prolonged protein starvation or to some metabolic deficiency of the kidneys.

Other details of the condition and progress require discussion as follows:

Lipids. With abundant butter and cream and occasional eggs in the diet, the blood serum was never cloudy and the cholesterol was well below 200 mg., with a normal proportion of esters. Limitation of lipoids or total fat, therefore, seemed unnecessary.

Kidney Function. At the outset, the fixed urine gravity of 1010 could not be altered by changes of fluid intake. After the high nitrogen retention was reduced, fluid drinking could be forced temporarily to a maximum of 2 liters, with diuresis temporarily up to 1600 or 1800 cc. in 24 hours, and gravity as low as 1004. The limit was set by feelings of fullness, liquid diarrhea and gain of 3 pounds of weight in 3 days. Loose edema in the usual locations was absent, but there was noticeable thickening and turgor of tissues, especially about the abdomen and thighs. The urination and diarrhea might be regarded as promoting elimination of toxic waste, but they were avoided as an over-driving of function. Dry diet entailing uncomfortable thirst for 3 or 4 days in succession has failed to concentrate urine beyond a gravity of 1012. Irrespective of variations of volume, about one-third is excreted during the twelve daytime hours and two-thirds during the twelve night hours. With drinking regulated according to comfort, the urine volume is about 800 or 900 cc. in 24 hours, with gravity of 1004 to 1010.

This spontaneous regulation has been adopted as making the least strain of function. The diet, therefore, must not provide excretory products in excess of this capacity. A specific improvement of kidney function would be the most desirable result, but there has been no sign of it within the six-month observation period. There has likewise been no clearing of albumin or casts.

Edema. In contrast to the retention from forcing of water alone, any trifle of salt in the diet makes typical edema of face and ankles. Hydremia has not been indicated by any changes of blood counts with either salt or forced fluid.

Hypertension and Tachycardia. The blood pressure under ordinary active conditions has been mostly 170/80, and the pulse rate about 100. The patient maintains that these figures are normal for him; that he has had them as long as he can remember, including observations at the time of an appendectomy in 1931. But I have one chance record of 120/70 in June 1942, and lack of mention of the pulse rate indicates that nothing abnormal was noticed. Both pressure and pulse can still be reduced almost to normal by brief rest. They are kept up by work and a nervous constitution. They have been improving under treatment, in spite of undesirable cigarette smoking. Theoretically, the treatment should include rest, and it is a question whether stress and tobacco and their cardiovascular effects will be a factor of progressiveness.

Anemia. Red cell counts of approximately 2,800,000, with 8 gm. or 54 per cent of hemoglobin, remained remarkably constant throughout the uremia, the protein starvation, the increased protein ration and the fluctuations of edema. Liberal anti-anemic medication and vitamines have been supplied constantly. Repeated moderate nosebleeds were among the uremic symptoms, but they presumably did not cause the anemia because their cessation did not alter it. Protein deficiency could conceivably prevent the upbuilding of blood, as of other protein tissues, but starved normal persons have no such degree of anemia. Nephritic anemia seems to represent an undefined role of the kidney in intermediary metabolism. Hydremia seems to be excluded by the figures of 5.0 per cent serum albumin and 2.3 per cent globulin. I can foresee no danger of visceral degenerations with this normal quantity and ratio of serum proteins. The latest blood count, showing increase

to 3,020,000 red cells and 8.5 grams of hemoglobin, marks the small limit of improvement to date. The yellowish tinge of the complexion is somewhat less than before.

Sugar Tolerance. Two features are noteworthy. First, though this treatment is based on the principle of diabetic treatment before insulin, it would not have been possible without insulin, that is, the protein metabolism cannot be reduced to a minimum without ample calories of fat and carbohydrate, which necessitate insulin. Glycosuria here is a poor guide because of the impaired renal permeability. One peculiar aid in guidance is the occurrence of chest pains whenever there is any considerable hypo- or hyperglycemia. They are perceptibly different from the pains caused by salt, and they are cured quickly by small additions of sugar or insulin. Also, a normal-appearing nutritive state can be maintained, but any marked obesity is impossible, because with the low protein the patient finds himself scarcely able to eat two thousand calories per day over any long period.

Second, the previously mentioned influence of renal impairment[14, 29] upon carbohydrate assimilation seems evident in this case. In the earlier years the insulin requirement ranged from 65 to 80 units daily. During the past fifteen years it has gradually diminished, reaching 35 units before the uremia and 25 to 30 units at present, in spite of the present exceptionally high intake of honey, jelly, cane sugar and cornstarch. Another role of the kidney in intermediary metabolism seems evident. It is also interesting that undernutrition diets have improved diabetic tolerance ordinarily by reducing adipose tissue, whereas the diet in this case has maintained adipose tissue while reducing the tissues which actively metabolize sugar.

Endogenous Metabolism. Creatinine is an index of renal excretory function and also of endogenous protein metabolism. One aim of the present treatment was to reduce blood creatinine by reducing the tissues that produce creatinine. The reduction of blood urea nitrogen to about 50 mg. and of the creatinine to 7.6 mg. with the long protein starvation has been mentioned. There being no morbid fear of creatinine as such, and the quality of protein being important with minimal rations, the subsequent diet ordinarily included some meat. As the protein was gradually increased from

15 to 30 gm. daily, nitrogen analyses of urine and feces indicated considerable storage by the protein-starved tissues even with the very low intake. Muscular strength improved correspondingly. Instead of the unqualified welcome given by Borst and all previous writers to this combination of positive nitrogen balance and clinical improvement, the difference of the present concept was shown by a notation in the record that this development called for suspicious watchfulness. The anticipation was fulfilled when the blood urea nitrogen remained at only 54 mg. while the creatinine had risen to 15 mg. per cent. It was not reduced by two weeks of creatinine-free diet or by increased water drinking for diuresis. There was a return of persistent vomiting and several nosebleeds. The new concept is that this change represents not progression of kidney disease but increased endogenous metabolism due to increment of body protein. The direct dietary protein was successfully disposed of, as shown by the absence of a rise of blood urea. The known endogenous product, creatinine, may perhaps typify accumulation of unknown metabolites of possibly more toxic character. At least, there is the evident burdening of a renal function with an endogenous substance resulting from building up the protein mass of the body. Clinical symptoms ceased with halving of the protein ration for two weeks. With resumption of 30 gm. protein daily, there is a precarious combination of high creatinine, mild acidosis and rare vomiting or other minor disturbances. A watch is being kept to decide whether this overload is sufficient to cause progressive renal deterioration, and, therefore, whether the body protein and strength must be reduced in the interest of protecting the kidneys.

Present Condition. The patient is energetic in business, misses no time from work and is regarded by his associates as healthy. The anemia and moderate phosphate acidosis have been mentioned. Up-to-date reports on the blood are as follows: red cells 3,020,000, hemoglobin 8.5 grams; serum albumin 5.0 and globulin 2.3 per cent; urea N 46, creatinine 14, uric acid 5.3, calcium 9.2, phosphate 7.4 mg. per cent; plasma bicarbonate 42 volumes per cent; serum sodium 122.8, potassium 5.8, chloride 100 mEq. per liter.

Here I am able to present the patient, who drove his automobile from New York to Atlantic City, accompanied by his wife and

mother. The yellow tinge of the complexion is now only slight. Doctors Joslin and Root may perhaps judge that his appearance is better than when they saw him in March. A little vomiting occurring perhaps once a month is stopped by a trifle of salt, and the slight diarrheal tendency is restrained with a little calcium lactate. The liability to anginal pains is controlled. He is hungry for protein, and desirous of knowing if representatives from the great medical centers can offer him any better prospects. I wish they could dissuade him from smoking.

COMMENTS ON PROBLEMS

1. Nobody has yet established the actual protein minimum on which human life can be maintained indefinitely. It may involve selection among amino acids. It is questionable whether high non-protein calories can be permanently consumed with this minimal protein. It is improbable that the lowest limits, which may maintain life, will always maintain working power. The therapeutic principle, if valid, should obviously be applied in the earlier stages, before these severe restrictions are necessary.

2. Nevertheless, there is encouragement for blood dialysis methods, now used in acute renal failure, to be extended also to the extreme stages of chronic uremia, in the hope that if the crisis can be tided over by repeated emergency measures, the protein mass and endogenous metabolism may gradually fall to an amount which the remaining kidney function can carry. There will doubtlessly be instances of function too low to be compatible with life at any level.

3. The principal general question is of prognosis. If survival is extended, can it be indefinitely, to the extent of a full lifetime? Can the now fatal forms of chronic nephropathy be added to the list of diseases which can be truly arrested by adequate relief of functional strain, at any stage? Resistance to progression may be actually greater than in diabetes. Numerous clinical examples show that the renal-vascular apparatus is remarkably tolerent of prolonged moderate elevations of blood nitrogen, pressure, anemia, also proteinuria and casts and the burden of near-maximal activity for twenty-four hours every day. Also, numerous kidney cases remain practically stationary, or they recover spontaneously in a manner unknown in diabetes. Therefore, the degree of abnormal

stimulation which makes or does not make progression is a problem, and there may be individual differences of sensitivity, just as in diabetes.

4. The most effectual kind of stimulus is also to be learned, whether toxic (nitrogenous), osmotic or intermediary metabolic. If blood nitrogen can be lowered by increased fluid supply, is there more harm in the chemical over-stimulation or the forced water diuresis? Will it be possible to disprove the tradition that sustained blood creatinine at the levels shown means fatality? In such a severe case, the theoretical functional relief might require practical invalidism, and, if necessary, this sacrifice will be made in the form of still lower protein and other restrictions. The present treatment provides a narrow margin for practically normal activity, by transgressing the theoretical principle in a gamble that the renal-vascular function will be resistent enough to withstand the indicated degrees of blood nitrogen elevation, nervous stress with its hypertension and tachycardia, perhaps also intermediary metabolic factors, plus the unnecessary danger of incorrigible chain-smoking of cigarettes.

5. The pathologic problem is fundamental. Recovery is absolutely limited by the impossibility of new formation of glomeruli. But, if such cases in general can be arrested, the interpretation must be that kidney disease may be initiated by some infectious or toxic injury but the subsequent progressive processes pictured by pathologists are due to functional overstrain. They are thus on a par with the hydropic degeneration of diabetic islands. The animal experiments showing progressive renal pathology produced by diet are likewise significant. This may be a more demonstrable, and, therapeutically, more hopeful explanation than allergic sensitization.

Material for a broader demonstration of the therapeutic principle in renal and certain other metabolic disorders is needed. All that is available now is the single relatively brief observation, that a case was progressing rapidly downward during six to twelve months to a critical uremic stage, and in the subsequent six months of incomplete sparing of function, there has been no apparent further progression.

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DRUG ACTION ON UNDERDEVELOPED AND DAMAGED BRAINS

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Differences between the action of drugs on children, compared with their action on adults, have been described since Falck's first observations in 1884. If a child is a smaller edition of mankind as compared with adults, then children always would need an adequately smaller dose of any drug. As a matter of fact, a child is and his reactions are in many ways different from the adult's, and is the reason for the development of pediatrics as an important art of medicine.

This is substantiated by the high tolerance of the newborn to some severe poisons. Experiments by Reiss and Haurowitz have shown that it takes but seconds to kill grown rats in an atmosphere of illuminating gas, carbon monoxide, cyanate or by strychnine, whereas newborn rats under the same conditions or by the same dosage survive for a long time. However, newborn and adult rats alike die quickly by chloroform. Drugs which interfere with respiration are more dangerous for adult animals than for the newborn. The reason is that carbon monoxide or cyanate interfere with oxygen utilization, and strychnine convulsions with the action of respiratory muscles, whereas chloroform, primarily a cell poison, acts on adults and newborn in the same period of time. This is true for rats and has to be assumed insofar as children are concerned inasmuch as they have often been the only survivors in a gas disaster which has killed the grown members of a family. The newborn also survives asphyxia much longer than adults. On the other hand, guinea pigs, which are born as "complete fellow citizens," are killed by carbon monoxide in the same time, whether newborn or adult (Glass and co-workers). The difference lies in the stage of development of the brain, which is completely developed in the newborn guinea pig, but, definitely, is not completely developed in the newborn child. Kabat has shown also that inhibition of brain circulation is tolerated more readily by newborn animals as compared with adults. The reason for the tolerance of asphyxia by the newborn for some time is that the newborn can metabolize

carbohydrates in an anaerobic way by glycolysis or fermentation. Warburg has demonstrated this process in fetal tissues, as well as in cancer cells or in any fast-growing tissue. The developed, well myelinated central nervous system is the only organ which cannot do without oxygen, even for a very short time.

Large areas of the central nervous system in the newborn are underdeveloped (Helmreich, Connel). The pyramidal tract is the only tract of the spine which is not completely developed at birth. In the medulla only the anterior part is myelinated at birth. In the first few months of life the myelin sheaths increase considerably in quantity and thickness. The pyramidal tract generally is well-developed by the end of the fourth month. Only the following areas of the brain are at least partly myelinated at birth: the central gyri, the lobus paracentralis, Heschl's convolutions, the neighboring parts of the superior temporal gyrus, the occipital pole, the area around the calcarine fissure, the hippocampus, the striae Lancisi, the substantia perforata anterior, the frontal lobe, Broca's convolutions, the area below the parieto-occipital fissure and the part below the gryrus angularis. Kaes mantains that the process of myelinization does not stop before the fourth decade of life.

At birth the histological picture of the cortex reveals a relatively greater number of cells, all approximately of the same size. The pyramidal cells cannot be distinguished. Dendrites are not found until weeks after birth. DeCrinis has shown that in the motor region dendrites are completely developed within eleven months, in Broca's convolutions within seventeen months, and in the frontal lobe within four years. The mental development of the child runs parallel with the development of the nervous system. When the infant is unable to walk, to talk or to react to his surroundings, it is not lack of practice, but a deficiency in the related nervous tissue. DeCrinis states that the instrument has to be built before it is possible to play it. It is equally surprising that these new instruments can be used so well the moment they are developed. Outside stimulation accelerates myelinization. It is retarded in the optic tract, in an eye that is experimentally kept closed as compared with the open eye (Ambronn and Held, Langworthy).

The effect of drugs on well-developed parts of the brain is stronger in infants than in adults because of the weak inhibitory effect of the cortex in young children. Spiegel, Miller and Oppen-

heimer claim that the olfactory tract is a dominating part in the inhibitory action of the cortex.

Drugs which act on undeveloped parts of the brain can be given to young children in astonishingly large doses.

There is a striking similarity between the effect of drugs on newborn and on decortisized animals. Thus, cocaine causes convulsions in adults, but not in the newborn, and does not act as an excitant in decortisized animals (Meyer, Gottlieb and Pick). Ephetonine is a stimulant of the cortex, but depresses decortisized animals (Moritsch) and acts as a hynotic on young children (Bonsanigo). Atrophine in large doses causes excitement, except in infants who often are put to sleep (Krueger).

Drugs acting on the brain are not the only ones that show such differences. They are very striking in the autonomic nervous system. The branches of the autonomic nervous system, the sympathetic or adrenergic, and, the parasympathetic or cholinergic, are in general antagonists and show an elaborate balance. Eppinger and Hess claimed that some people have a preponderance of the parasympathetic system. They tolerate stimulation of the sympathetic system very well, but react strongly to parasympathetic drugs. This is also true of newborn children, who tolerate atropine in large doses, but react strongly to physiostigmine. The young tolerate sympathomimetic drugs, such as ephedrine, etc., in very large doses, but react very strongly to epinephrine. This contradiction can be explained by the development of the autonomic nervous system. The vagus nerve, complete at time of birth, is stimulated easily and lacks the inhibitory break of the cortex. Welsh and Hyde found an even stronger effect of potassium on the newborn in acetylcholine production. The sympathetic part in the newborn shows underdevelopment. The sympathetic ganglia are underdeveloped (Helmreich), and the adrenals contain minimum amounts of epinephrine (Danish, Schmorl, Kramer). The effect of ephedrine, benzedrine, etc., has been explained by Gaddum as destruction of the enzymes which destroy epinephrine. They, therefore, increase and prolong the action of the natural epinephrine. The effect on the newborn is weak as there is no epinephrine present which has to be protected from destruction. Epinephrine itself, of course, has a strong effect, which often is different from the results seen in adults, and resembles adrenalin effects seen in animals

following strong vagus stimulation (Kolm and Pick). Vomiting following adrenaline injection occurs in the newborn only. The vagotonic trend of the newborn suits his requirements very well. Cannon has stated that the sympathetic system is of great importance in "flight or fight," conditions which do not concern the newborn who sleeps most of the time.

The anatomical development of the brain is not the only point of influence in drug action. Metabolic conditions in the newborn also differ from those in adults. We have mentioned obtaining energy by anaerobic ways of fermentation. Unfortunately, however physiology of the brain function is not completely understood. Even the ways of action of the peripheral nerves are in a stage of intensive discussion. It has been known that electric currents stimulate nerves as long as electricity itself has been known. But the famous experiments of O. Loewi have shown that chemical processes also play an important role in nerve activity. Acetylcholine is produced at cholinergic synapses, norepinephrine or epinephine at sympathetic synapses. Nachmansohn claims that acetylcholine is not produced at synapses only, but on the entire nerve fibers, and action currents are the chief elements in nerve stimulation.

Acetylcholine, as well as epinephrine or norepinephrine, are quickly destroyed by enzymatic processes. The quick regulation of the autonomic nervous system would be impossible without this destruction.

The mechanism of function of brain activity is not well understood. Dale and his co-workers claim that acetylcholine is produced at some synapses of the brain; others are sympathetic. But they were unable to identify the produced substance (Feldberg). I do not doubt that epinephrine-like substances are effective in brain activity, as the sympathomimetic drugs, such as ephedrine, cocaine, benzedrine, are all brain stimulants and are considered substances counteracting the epinephrine destroying enzymes. v. Euler long ago proved that epinephrine is found in brain tissue. M. Vogt could demonstrate the presence of sympathin (epinephrine and norepinephrine) in some parts of the brain.

Acetylcholine production depends on the presence of glucose as well as of oxygen. Without these two substances brain activity stops immediately. Nachmansohn and Machado found an enzyme,

cholin acetylase, which synthesizes acetylcholine in the presence of adenosin-tri-phosphate in aerobic as well as anaerobic conditions. Some amino acids are also necessary for the normal acetylcholine cycle, especially glutamic acid (Nachmansohn, John and Waelsch). This amino acid was introduced for the treatment of epilepsy (Price, Welsh and Putnam) and of oligophrenia (Welsh).

Nucleoproteins also play an important role in brain activity as they are present in decreased amounts only in ganglia of psychotic patients (Hyden and Hastelius).

We, therefore, have a long list of substances which are important in brain activity and could be tried for therapeutic purposes, just as glutamic acid has been tried. This substance has some effects which may not have met all expectations; but something happens in a brain with glutamic acid therapy. We had here twin brothers with phenylpyruvic oligophrenia, both extremely low grade boys, who did not show any reaction even to a venepuncture. One of them was treated with glutamic acid for some weeks. A reaction cannot be denied, even though it was not too pleasant. He reacted wildly to stimuli, fought like a tiger against a venepuncture, became aggressive, and finally had to be transferred to a state hospital.

If we assume that the important role of glutamic acid is the acetylcholine formation, then actylcholine itself should have an even stronger effect. The list of substances which could be tried in a similar way include acetylcholine and the more resistant cholinergic drugs, such as doryl or mecholyl, or the anticholin esterese group of physostigmine, prostigmine, etc. The same could be said for the sympathetic group.

We have given, with this in mind, prostigmine and ephedrine simultaneously to some of our mentally retarded patients, drugs which act by inhibition of the enzymes which destroy acetylcholine and epinephrine, respectively. The first results are very promising and will be reported later in full detail.

At present we are more informed regarding damaging substances than we are concerning helpful drugs in brain activity.

There are at least two fields of information in regard to the damaging effects of chemicals on brain activity. One is phenylalanine. Natural metabolic errors have often improved our physiological knowledge. This disease, phenylpyruvic oligophrenia, was

described first by Foelling, in 1934. There are three leading symptoms in this disease, that of familiarity, of mental retardation and of a lack of the enzymes which oxidize phenylalanine to tyrosine. Bickel has shown that phenylalanine is "the" damaging substance of the brain. This is not as surprising as it seemed to be to many physicians.

Abderhalden and Tetzner have shown, many years ago, that r-phenylalanine is a severe nerve poison. The physiological l-phenylalanine of proteins in their experiments was harmless as it was converted in the body very quickly to the non-poisonous tyrosine. In our patients the physiological l-phenylalanine becomes dangerous as it is not oxigenated. The mechanism of action of phenylalanine on the brain is not known. A diet free of phenylalanine is helpful in the very young only; it is, therefore, assumed that it causes lasting damage to the brain which cannot be overcome by restriction of phenylalanine intake.

Modern brain surgery has revealed another deteriorating effect on the brain. It was described by many authors that removal of an epileptic focus does not only cause cessation of convulsions, but is accompanied by mental improvement. Krynauw even removed the complete brain hemisphere so that no damaged or pathological tissue remained; he found mental improvement in all his patients. This can be explained only by a deteriorating effect of damaged brain tissue to its surroundings, probably by some hitherto unknown substances.

Little progress in our knowledge of brain physiology was made until the present time in providing us with effective remedies for brain diseases. The pleasingly long list of drugs for such diseases, with a few exceptions only was found by chance. The drugs used in brain diseases can be divided into three groups: the anti-epileptics, the convulsants and the new group of ataractics.

The first drug to be found useful in epilepsy was bromine, which was introduced for this purpose by Locock in 1857, who tried it first as an antiaphrodisiac, because epilepsy was thought to be the result of masturbation (Umna). It remained for a long time the only drug known to be effective in epilepsy. The action of bromine is in general its exchange for chlorine. The importance of the salt metabolism for nerve activity is well-known. The shift of sodium, potassium and chloride has been studied (Ecles), but the

relation to epilepsy and to antiepileptics is not quite clear. Swingard claims that the electroshock seizure threshold is more closely correlated with extra-cellular sodium and chloride concentration than with potassium or water. But epileptic fits, on the other hand, are instigated by huge water intake.

In 1912 Hauptman introduced luminal for treatment of epilepsy. It is even now one of the very few barbiturates with an anticonvulsive effect in dosage below the hypnotic dose range. Chemically related drugs used in epilepsy are mephobarbital or mebaral, metharbital or gemonil, and primidone or mysoline. Many drugs useful in epilepsy have been found as results of Merritt and Putnam's experiments in which they studied the influence of many different chemicals on electrically induced convulsions in animals. Here we find the hydantoin derivatives diphenylhydantoin or dilantin, its sodium salt, and mesantoin. Oxazolidine derivatives, such as tridione or paradione, are chiefly used in petit mals. Other new antiepileptics are phenacetyl urea or phenuron, hibicon, prenderol. A chart from Unna's article will give a picture of their merits in different forms of epilepsy.

Studies have been made about the mechanism of action of the antiepileptics on brain activity. An effect of the barbiturates on the acetylcholine cycle is not demonstrable directly. In prolonged treatment the cholinase in the blood stream decreases (Schuetz, Radouco-Thomas and co-workers). But relationship of antiepilep-

	DRUGS*					
Effect:	*Phenobarbital*	*Mebaral*	*Dilantin*	*Mesantin*	*Tridione*	*Menurone*
Raising threshold of electroshock						
In normal animals ..	++	+	0	+	+	+++
In hyponatronic animals	++	++	++	++	++	+++
Modifying maximal electroshock seizures.	+++	++	++++	++++	+	+++
Preventing psychomotor seizures	+	+	0	+	0	++
Raising threshold of pentyline tetrazol induced convulsions ..	+	++	0	+	++++	+++

*From Drugs in Epilepsy and Hyperkinetic States. Unna, 1954.

tics on brain physiology remains obscure. Unna is right in saying: "no specific effect on cell metabolism has been demonstrated with

any of the antiepileptic agents in concentrations which may be expected from therapeutic doses in brain tissue. . . . Since these drugs prevent the spread (detonation) of abnormal discharges, they presumably act on normal neurons, protecting them from the invasion by seizure activity of abnormal foci."

The next group of drugs are the convulsants. Sackel introduced the insulin shock therapy for mental diseases. This was replaced later by some less dangerous convulsant drugs, such as picrotoxin and benzedrine, etc., (Meduna) but is now generally replaced by electric shock (Cerletti).

The underlying physiological mechanism is not quite clear. Weil-Malherbe found an increase of epinephrine and of norepinephrine in the blood following shock and infers that "activation of the sympathetic system plays an important part in the therapeutic efficiency of convulsive treatment, be it as an unspecific result of stress or owing to a more circumscribed stimulation of specific centers in the hypothalamus or elsewhere." Fetter claims a cholinergic effect, and Sackler and co-workers even discuss histamine liberation as an activating mechanism.

The last group is a list of drugs which is used for treatment of pathologically agitated patients, for which the name "ataractics" has been proposed.

The first used drug of this group was mephenesin, tolserol or oranixon, which was introduced for the production of weakness and flaccidity of skeletal muscles by a spinal action, different from the myoneural action of curare. It causes a lassitude with sedation, but the effect is of short duration only. It is the most harmless, but also the least effective of these drugs.

The next drug is rauwolfia, an Indian plant which has had its place in Indian folk medicine for centuries. It was introduced into modern medicine for its repressive effect on blood pressure. Some alkaloids have been isolated from rauwolfia. The used preparations have different names, such as raudixin, serpasil, rauwiloid. Some side effects on the central nervous system were observed, and the drugs were used with very good results to quiet excited patients. The blood pressure has to be controlled for their depressing action.

The last, most promising drug is thorazine, which was introduced as an antihistaminic. Later its antiemetic effect was observed.

Now its chief indication is its calming effect on agitated patients. The effective dose is sometimes quite high. Destructive effects on bone marrow and agranulocytosis following thorazine therapy is possible as is always the case with drugs of chemical complexity. But this seems to be an extremely rare occurrence.

The mode of action of these drugs has not been explained. The quieting effect on pathological excitement could be connected with stimulation of the inhibitory parts of the cortex, but, also, an influence on autonomic transmiters is possible. It is worth mentioning that the rauwolfia alkaloids have been proven to act as adrenergic blockade (Nickerson), whereas thorazine is a strong antiemetic which impresses an anticholinergic effect. Perhaps the best results will be obtained by combining these two drugs.

Finally, fever therapy may be mentioned which was introduced by v. Wagner-Jauregg for the treatment of general paresis. The effect is probably a direct one on the spirochetes and has nothing to do with brain activity.

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FIRST RESULTS OF HIBERNATION IN BABIES AT THE SAINT VINCENT DE PAUL HOSPITAL. (Semaine hop., 30:173-175, Sept. 10-14, 1954). Seventeen babies were treated with chlorpromazine (10-[γ-dimethylaminopropyl] - 2 - chlorophenothiazine hydrochloride) associated with promethazine (Phenergan) hydrochloride and meperidine (Dolosal) hydrochloride or phenobarbital (Gardenal) given in intravenous or intramuscular injections. All the babies were resistant to the usual forms of therapy; they had various diseases, but all had the following symptoms: hyperthermia; nervous signs, such as convulsions, excitation, or coma; and vascular collapse, with cyanosis, absence of pulse, or hypotension. Besides these major indications, three babies were put in hibernation for suffocating dyspnea caused either by the sudden enlargement of a pulmonary bleb or by a pyopneumothorax. In this series, hiberation was achieved through the use of drugs alone. Antibiotics, plasma, and rehydrating solutions were also adminstered. Good results were obtained in seven infants; in general, these were the children in whose cases intervention was made early in the course of the disease. The effect of artificial hibernation was to keep the patient alive until treatment of the basic disease process could take effect or surgical procedures be performed.—*J.A.M.A.*

UNUSUAL COCCIDIOIDOMYCOSIS CASES*

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In an endemic area for coccidioidomycosis in which this writer lives, he feels quite fortunate in seeing many interesting and unusual cases gravitate to the Kern General Hospital. In fact, whenever a case of coccidioidomycosis is reported in current literature elsewhere in the country, the chances are we have seen such cases repeatedly, but considered them too commonplace to report as "unusual." The following cases are reported because they are unusual, and secondly, because of the initial use of new drugs in treating them.

CASE REPORTS

Case 1. An eleven-year-old white boy had cut the second toe of his left foot. It would not heal under various antibiotic therapy but gave off a continuous discharge of greenish matter. When the regional glands of the inguinal became swollen and tender, he was admitted to the Kern General Hospital. The important contributory points in his history were: 1. He was living in a highly endemic area (Southern San Joaquin Valley). He never had a temperature, lassitude, cough, nor loss of weight prior to and during this infection. His general physical examination was essentially negative except for the left foot, and inguinal area. The laboratory reports revealed a negative tuberculin skin test, and a three plus coccidioidin skin test. A chest x-ray was essentially negative. X-ray of the bones of the foot did not show destructive lesions nor granulomas of the bone. Cultures from the drainage of the foot and the broken down inguinal glands showed the fungus of coccidioides immitis. Spherules were also seen on a wet mount. The white blood count was 11,500. The hemoglobin was 12.3 grams (85 per cent). The differential count revealed polymorphonuclear cells 60 per cent, lymphocytes 29 per cent, monocytes 5 per cent and eosinophiles 6 per cent. The Kline test was negative. The urine test was negative. The first complement fixation was 4+ in 1:2, 4+ in 1:4 and 4+ in 1:8 dilutions. The precipitins were negative. This case was diagnosed as a primary coccidioides of the

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foot. The patient was placed on ethyl vanillate of 16 grams daily, and sassafras tea.[1, 2] After three months' therapy, the complement fixation dropped: 4+ in 1:2, + in 1:4 and 0 in 1:8 dilutions. The patient did well and the parents moved the child to Los Angeles. The mother wrote that a surgeon wished to remove the child's inguinal glands, but the author was not in favor of such treatment. (See Fig. 1).

Case 2. A two-year-old Mexican male child was first admitted to the Kern General Hospital in April 1954 because of irritability and vomiting. He had been examined often in the clinic for diarrhea and upper respiratory infections, and also because of a bony prominence on the right frontal area. In May 1954, the child was hospitalized for pneumonitis. He was unresponsive to antibiotics. He had a positive coccidioidin skin test and a negative tuberculin test. His coccidiodal serology was four plus in dilution of 1:64. He was a highly irritable child and cried continuously. His physical examination was negative, except for the prominence on the right frontal area, and a fusiform swelling of his left middle finger (spinaventosa). X-ray of the finger showed osteolytic changes. This lesion broke down and drained. Spherules of coccidioides were noted on wet mount obtained from this lesion. X-ray of the chest still showed much haziness in both lung fields. Because of repeated vomiting, meningitis was suspected. A spinal tap was done and it revealed 276 cells with lymphocytes dominating the count. A 30 mgm. per cent sugar was obtained. The spinal fluid on setting grew out the fungus of coccidioides. The diagnosis was severely disseminated coccidioides of lungs, skull, digit and basilar meningitis. (See Fig. 2).

He first was placed on ethyl vanillate but vomited it as well as his food. The vomiting was attributed to increased ventricular pressure.

The sodium salt of cinnamic acid[2, 3] then was started; a 5 cc. of 5 per cent solution was given intramuscularly every four hours, then gradually increased from 10 cc. to 20 cc. Shortly thereafter, 500 cc. was given intravenously in 24 hours. The blood cinnamic acid test showed 4 milligrams per 100 cc. The invitro test showed that it kills coccidioides at 30 micrograms per milliliter. The child's complement fixation was 2 plus in 1:128 dilution. The hemoglobin was 12 grams or 77 per cent. The erythrocytic count was 4,320,000.

The sedimentation rate was 42 mm. with a hematocrit of 36 per cent. The white count was 13,600 with 63 segmenters, 32 lymphocytes and 5 monocytes. The urine was essentially negative. The child cried continuously, not happy for a moment while in the hospital. He was undernourished, and appeared chronically ill. His head was slowly becoming enlarged. His extremities were atonic. He had a thin chest wall. He had tight hamstring muscles on neurological examination. He expired after being hospitalized for six months.

Case 3. A seven-year-old colored female child was admitted to the Kern General Hospital because of a lump in the lower portion of the back of four months' duration, and who limped while walking. X-rays, taken as an outpatient, revealed osteoporosis of the third and fourth lumbar vertebrae. Her past, contributory history revealed that she had a positive coccidioidin skin test and a negative tuberculin test. She had had a pulmonary coccidioides with a complement fixation of one plus in 1:4 dilution, but the precipitins were one plus in dilutions of 1:40. She was admitted to the orthopedic department, placed on a Bradford frame, and later in a body cast. She became progressively worse. Her abdomen became so enlarged that the cast had to be removed. Serial x-ray showed more osteolysis of the lumbar bones, and a large abdominal shadow near the vertebrae was thought to be an abscess. An exploratory laparotomy was done, the abscess was opened and drained to the right flank which resulted in a fistulous tract. Soon, the navel began to ooze pus, and a new lesion opened from the peritoneum. Multiple coccidioidal, broken down, granulomatous lesions began to occur at the left buttock. The patient was small for her age and had a thin chest wall. Physical examination showed that she had a ptosis of the right upper lid. The heart and lungs were noncontributory. The abdomen was ballooned, tenderness and a soft tissue mass was felt at the fourth and fifth lumbar areas. A large sinus, midway on the right flank, was noted. The naval exuded green pus, and the same matter was observed on the left buttock. She had tight hamstrings, and could not extend her legs. The child spiked high temperatures for a few months, and it seemed that each day would be her last day in the hospital. She had a short trial with ethyl vanillate, but showed no response. Then, she was placed on diethylstilbestrol,[4] and

given as much as 75 milligrams per 24 hours. Her temperature became normal and her breast enlarged; the lesions continued to drain; her abdomen, with its coccidioidal peritonitis,

Fig. 1 (Upper left) Primary coccidioides of skin. Fig. 2 (Upper right) Showing spina ventosa. Fig. 3. (Lower left) Peritonitis with oozing from navel and granulomatous pelvic lesion. Fig. 4 (Lower right) Draining sinus with 3rd and 4th lumbar vertebrae.

remained distended; her legs were drawn up and very atrophic. Her complement fixation was 1+ in 1:256 dilution. The coccidioidin skin test was now negative, which was a bad omen. The hemoglobin was 9 grams or 58 per cent. The erythrocyte count was 3,680,000; the leukocyte count was 13,400 with 57 per cent segmenters, 2 per cent eosinophiles and lymphocytes 41 per cent. The urine was essentially negative. The sedimentation rate was 13 mm., with a hematocrit of 35 per cent. She was tried on para-aminobenzoic acid,[5] and reacted poorly. Her erythrocyte count dropped. She kept complaining of headaches. A cisternal puncture was done, and revealed a meningitis. It was attributed to the breaking through of the ostolytic vertebrae into the spinal canal. The child expired a few weeks later, after 13 months in the hospital. (See Fig. 3).

Case 4. A 22-month-old colored female child was admitted to the Kern General Hospital, December 21, 1953, because of a soft fluctuating mass in the occiput of 3-weeks' duration. An x-ray showed a granuloma of the skull.

On January 19, 1954, the patient had a 101° F. fever, and the right leg began to drag when she walked. A small mass was noted in the lumbar area.

Physical examination showed a moderately well-developed and well-nourished colored girl, not very much distressed but moderately ill. The skull showed a soft fluctuating mass, but not painful, and without heat. The only other contributory finding was the soft fluctuating mass in the area of the third and fourth lumbar spines. The x-ray revealed a granulomatous shadow on the skull, and destruction of the bodies of the third and fourth lumbar vertebrae. The coccidioidin skin test was one plus, and the Mantoux negative. A positive culture for coccidioide was obtained when the lumbar lesion broke. Spherules were also seen on wet mount. (See Fig. 4).

Para-aminobenzoic acid was tried but the red cell count was so reduced that it was discontinued. Ethyl vanillate was started on March 1954, and was gradually increased to 24 grams a day in divided doses. She has been on this therapy for over 16 months. The last x-ray of the vertebrae showed that the bone has healed but there still remains a discharge from the sinus area about the spine. Her complement fixation test has not changed. The coc-

cidioidin skin test is still positive so that the prognosis for recovery is promising after 16 months. Her hemoglobin was 10.5 grams, or 68 per cent; the red blood count is 3,490,000; the color index is 0.98; the white count is 10,600 with 44 per cent lymphocytes, polymorphonuclear cells 45 per cent, monocytes 7 per cent, and eosinophiles 4 per cent. The urine test was essentially negative. The child was released from the hospital on July 24, 1955.

DISCUSSION

Case 1 is highly suggestive of a primary extrapulmonary lesion. It is almost hard to say that it is a primary lesion even with Wilson's[6] criteria. The lack of pulmonary findings, the negative history would certainly suggest a primary skin infection of coccidioidal origin. With due respect to Wilson and this case, on postmortem examination, the author has seen coccidioidal skin lesion cases with retrohilar and paratracheal lymph glands that showed the spherules of coccidioides though the x-ray of the chest was negative, and the patient had died of some other condition. The patient was given ethyl vanillate[1] which has been in use clinically for 5 years on valley fever cases. Also, since showing that the oil of sassafras inhibits coccidioides at 500 micrograms per milliliter, he has been taking three ten-ounce glasses daily. There is no harm in giving this therapy. It is pleasant to take and it might do some good. It has been prescribed for all the author's primary coccidioidal cases and the disseminated ones. The patient's complement fixation dropped. In view of all visible laboratory and clinical findings, Case 1 is considered a primary skin infection of coccidioides, but, with a mental reservation.

Case 2 shows a classically progressive, downhill disseminated case of coccidioides. This severe pulmonary lesion did not resolve itself. The spina ventosa developed with terminal meningitis. He was unable to retain the ethyl vanillate, therefore, the sodium salt of cinnamic acid was used for the first time. Cinnamic acid was used as a liver function test in 127 cases by Saltzman and Caraway.[3] It is nontoxic and can be given intravenously and intramuscularly. Because it has never been administered over a long period of time, the dosage was increased slowly from 5 cc. to 10 cc. to 500 cc. of 5 per cent solution first intramuscularly, then intravenously. The blood test showed that the vitro level was never

reached. Large dosages had not been given. The necropsy report showed no deleterious side effects from the drug. Should another meningitis of coccidioidal origin show itself, it is felt that higher concentrations of 10 per cent to 20 per cent solutions of cinnamic acid could be given, and followed by the blood test.

A point in diagnosis is herein mentioned in passing. Smith[7] undoubtedly has done immeasurable work on serology associated with clinical cases, but now, we believe we have seen more clinical coccidioidal meningitis cases in the past 7 years in Bakersfield than have been seen in San Francisco, where it is not usual. No one has ever reported that which has been seen repeatedly in the past seven years at Bakersfield, that is, coccidioidal meningitis spinal fluid will grow out with a cotton looking matter if allowed to set at room temperature, sealed in with a cork. The author terms it "mother coccyx" as it resembles mother vinegar in appearance. Case 2 took over one month of setting, but it did manifest itself in the spinal fluid.

Cases 3 and *4* are remarkably similar, but the outcomes apparently are different. The "let alone" treatment of Case 3, that is, putting the patient on a Bradford frame, and then in a cast for the osteolytic lesions of the lumbar area, did not fare well. It is, in substance, the contention of Dykes et al.[8] that the majority of bone lesions, though chronic, will heal of themselves. Opinions differ; however, the protocols of the hospital records show that many of the cases reported were on my antifungal therapy and the authors did not think it of any merit to mention. I feel that the improvement shown by the different cases was due in substance to the drugs offered. One case mentioned of a completely healed disseminated coccidioidomycosis, that died of sympathetic blastoma had taken a drug called actidione. Dykes mentioned it as self-healing. Dr. Gifford, a pioneer in the field of coccidioidomycosis, requested the author to report that case, which was done. It is wrong to consider self-limiting therapy in bone lesions. The peritonitis phase usually is not too harmful. Three cases of coccidioidal peritonitis were observed and all recovered nicely, one with rest, and the other two with actidione. Clinical experience shows that most lesions of the skull respond more rapidly to therapy than extremities or vertebral lesions. Dennis et al.[10] substantiate this.

Ethyl vanillate has been used by the author for the past five

years, and the original mycology study was reported.[1] It is far from the perfect drug because of taste, expense, and the long, drawn-out therapy. Fiese et al.[11] and Dennis et al.[10] reported their experiences with ethyl vanillate therapy. It was gratifying to have others use this drug. There was some difference of opinion in the treatment of cases termed disseminated with ethyl vanillate, but time has proved that the drug offers some encouragement, though, as yet, it is far from being the "ideal" therapy.

The sodium salt of cinnamic acid requires more clinical trials before a true evaluation can be made.

SUMMARY

Four unusual cases of coccidioides are reported and therapy outlined. The author contends that the majority of osseous lesions of coccidioides are not self-limiting.

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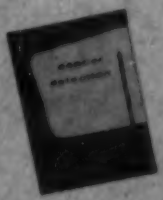

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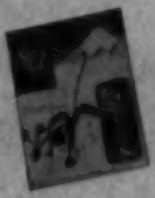

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